PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

16

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
1102865-0034		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US99/10750	14/05/1999	15/05/1998
International Patent Classification (IPC) or national classification and IPC A61K31/505		
Applicant APHTON CORPORATION et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 1 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
14/12/1999	17.08.2000
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Simm, M.D. Telephone No. +49 89 2399 7411

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US99/10750

I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-21	as originally filed				

Claims, No.:

1-9	as received on	06/06/2000	with letter of	05/06/2000	

Drawings, sheets:

1/3-3/3	as originally filed

2. The amendments have resulted in the cancellation of:

☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 8-9, in respect of i.a..

because:

☒ the said international application, or the said claims Nos. 8-9, in respect of i.a. relate to the following subject matter which does not require an international preliminary examination (*specify*):

see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-9
	No:	Claims	
Inventive step (IS)	Yes:	Claims	6
	No:	Claims	1-5, 7-9
Industrial applicability (IA)	Yes:	Claims	1-7
	No:	Claims	8, 9

2. Citations and explanations

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item I

Basis of the opinion

Reference is made to the following documents:

D1: EP-A-0 755 683 (CENTOCOR INC) 29 January 1997 (1997-01-29)

D2: AJANI J A ET AL: 'PHASE I AND II STUDIES OF THE COMBINATION OF RECOMBINANT HUMAN INTERFERON- AND 5-FLUOROURACIL IN PATIENTS WITH ADVANCED COLORECTAL CARCINOMA' JOURNAL OF BIOLOGICAL RESPONSE MODIFIERS,US,RAVEN PRESS. NEW YORK, vol. 8, no. 2, page 140-146

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 8 and 9 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Novelty (Art. 33(2) PCT) and Inventive Step (Art. 33(3) PCT)

D1 discloses a combination of immunotherapy of tumor with monoclonal antibody against the tumor associated antigen 17-1A with chemotherapy. The document suggests that the murine antibody treatment can be adjuvant to other forms of therapy including chemotherapy.
However, no synergistic effect is shown between both types of therapies and no emphasis is put on the suggested "adjuvant effect".

D2 refers to a combination therapy (chemotherapy and immunotherapy) for treating colorectal carcinoma comprising 5-Fluorouracil and Interferon-[SPEC0807]. The document fails to reproduce in patients the synergistic effect found in preclinical experiments.

The combination of a chemotherapeutical agent with anti-gastrin 17 immunogen is novel over the prior art. However, the combination of two known substances can only be inventive if a surprising effect is produced by such a combination. The experiments presented show a greater therapeutic effect of 5-FU/Leucovorin (page 17 and Fig. 4 and 5) when combined with anti-G17(1-9)-DT , and surprisingly the effect is even greater when reducing the dose of 5-FU/Leucovorin. This synergistic effect is not suggested or disclosed in the prior art.

However, claims 1-5 refer to any "chemotherapeutical agent". From the teachings of the present application it is not apparent that the alleged technical effect would occur with any chemotherapeutical agent, especially taking into account that this term covers any chemical substance used in therapy. Therefore, it appears that the technical problem is not solved over the entire scope of the claims and they lack an inventive step (Art. 33(3) PCT).

Claim 6 restricts the chemotherapeutical agent to 5-fluorouracil, leuovorin, cisplatin, tumor necrosis factor and proglumide. Thus, the subject-matter of this claim appears to be novel and inventive.

Dependent claims 3-5 and 7 do not contain any features which, in combination with the features of claim 2, meet the requirements of the PCT in respect of inventive step.

Industrial Applicability (Art. 33(4))

For the assessment of the present claims 8 and 9 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a

known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item VIII

Certain observations on the international application

The scope of claims 1-5 is defined by a broad term "one or more chemotherapeutic agents". The description provides support only for a number of chemotherapeutic agents (see page 6, last paragraph of the description of the present application), thus this claim lacks support by the description (Art. 6 PCT and PCT Guidelines C III-6). Furthermore, it appears that on the basis of the information given in the application as filed, the skilled man would be unable to extend the particular teaching of the description to the whole of the field claimed by using routine methods of experimentation or analysis because no other tumor growth factors are mentioned.

What we claim is:

1. A method for treating a tumor in a patient, comprising immunologically neutralizing a tumor-growth factor and administering to the patient an effective amount of one or more chemotherapeutic agents.

2. The method of claim 1, wherein the tumor is a gastrin-dependent tumor.

3. The method of claim 1, wherein the tumor-growth factor is gastrin.

4. A method for treating a gastrin-dependent tumor with a combination therapy, comprising administering to a mammal in need of said treatment a therapeutically effective amount of an anti-gastrin 17 immunogen, in combination with one ore more chemotherapeutic agents.

5. The method of claim 4, wherein the antigastrin-G17 immunogen is conjugated to Diphtheria toxoid.

6. The method of claim 4, wherein the antigastrin-G17 immunogen further comprises a spacer peptide.

7. The method of claim 4, wherein the antigastrin-G17 immunogen comprises a peptide consisting of amino acid sequence pGlu-Gly-Pro-Trp-Leu-Glu-Glu-Glu-Glu (SEQ ID NO.: 1 in the Sequence Listing).

8. The method of claim 4, wherein the chemotherapeutic agents are 5-fluorouracil and leucovorin.

9. The method of claim 4, wherein the antigastrin-G17 immunogen is administered prior to administering 5-fluorouracil and leucovorin chemotherapy.

10. The method of claim 4 or 9, wherein the chemotherapeutic agents are administered in several cycles during the therapy.

11. The method of claim 1 or 4, further comprising administering one or more booster immunizations.